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Averting Future Influenza Vaccine Shortages

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I am Walter A. Orenstein M.D., Director of a new program on Vaccine Policy and Development at Emory University and Associate Director of the Emory Vaccine Center and Associate Director of the Southeastern Center on Emerging Biologic Threats. Prior to joining Emory University in March 2004, I was Director of the National Immunization Program at the Centers for Disease Control and Prevention. I want to thank the Committee on Government Reform for the opportunity to address public health implications of the recent influenza vaccine shortages, assess strategies used to minimize their impact, and recommend potential steps that may be taken to avert future shortages.

I will briefly discuss my major recommendations for averting future shortages (Table 1), provide background for those recommendations, and discuss efforts made this year to take maximal advantage of the limited supply available.

Averting future shortages involves providing incentives: 1) to manufacturers to stay in or enter the US market, 2) to providers to order and administer influenza vaccine, and 3) to people for whom influenza vaccine is recommended to accept vaccination. A critical incentive for manufacturers is to decrease financial risk for vaccine that is produced but must be discarded each year since last year's influenza vaccine cannot be used for the following season. This can be accomplished through a "back-end guarantee" or "buy-back" program in which the Federal Government asks manufacturers to produce more doses than they usually would and pays the manufacturer at the end of the influenza season for doses that go unsold on the private market. For, example, if the usual production is 80 million doses and the Federal Government wants 90 million doses produced to cover more of the 188 million persons for whom influenza vaccine is already recommended, then the Government can guarantee the companies that they will pay some discounted price for each of the 10 million doses that may go unsold.

As a further incentive to the companies, an effort should be undertaken to increase demand for influenza vaccine and thereby increase the size of the market. This should include at least three components. First, a national educational effort directed at both the medical community and the public to understand the personal and public health benefit of influenza vaccine. Second, an adult immunization grant program, modeled after the successful childhood immunization program, should be undertaken which provides grants to states and localities to build immunization infrastructure for immunization of adults. This would include components such as staff who can provide technical assistance to health care providers to improve their performance, development of data systems to track and monitor vaccine supply and use, and measure immunization coverage, and personnel who can assist nursing homes in conducting immunization programs and outreach workers who can perform educational efforts. Third, influenza vaccine should be purchased by the Federal government and supplied to states for uninsured high-risk adults for whom influenza vaccine is recommended to minimize financial barriers to access and increase vaccine use.

Incentives for providers include provision of free vaccine for their uninsured patients decreasing their financial risk of potentially ordering vaccine that goes unused, access to technical assistance from state and local health departments, and provision of educational materials for their patients from those health departments.

Incentives for patients include removing the financial barrier for vaccine purchase for the uninsured and provision of this vaccine in convenient locations.

Influenza is a serious health burden accounting for an estimated 36,000 deaths and more than 200,000 hospitalizations annually. Reducing the burden of influenza through vaccination is associated with much greater challenges than any of the other diseases against which vaccines are routinely recommended. There are a number of scientific and programmatic obstacles that must be overcome.

The influenza virus frequently mutates or changes. The more the virus changes from strains circulating the previous year, the greater the number of people who become susceptible, and the greater the potential for severe epidemics. Because the virus changes, the influenza vaccine is usually different each year from the previous year.

The process for making influenza vaccine is complex. It requires fertilized or embryonated chicken eggs, selection of which strains should go in the vaccine, assuring those strains grow in the eggs, producing and testing each individual stain and combining vaccines against each of three types of influenza viruses into a single dose of vaccine. Selection of strains, which usually occurs by February or March of the preceding season, to actual distribution of vaccine to providers, takes about 6-8 months. The process is not very flexible and has difficulties in meeting surges in demand or making changes in the vaccine should newer emerging and circulating strains be identified late in the process. Demand forecasting usually must occur many months prior to actual production and distribution.

Because of the need for rapid identification of new strains, a comprehensive global surveillance system is required. Most new strains have their origins outside the United States, particularly in Asia.

In addition to the scientific challenges noted above there are a variety of programmatic challenges. The fragility of the vaccine supply, itself, serves as a disincentive to promote its use. Health care providers and others may be reluctant to promote vaccine if they cannot be assured they will receive needed vaccines. Thus, solving the supply problem for the long term is critical to efforts to try to enhance prevention of influenza beyond current levels and avert backsliding.

The CDC estimates that approximately 188 million Americans should be vaccinated annually against influenza. However, even in years with supplies adequate to meet demand, only about 80-85 million persons are vaccinated. Thus, there is a critical need to expand coverage. This will not only improve prevention but will increase the market and hopefully stimulate more manufacturers to enter the market.

A further programmatic challenge is the relatively short vaccination season. Influenza vaccine is typically administered in October and November. While efforts have been made to extend the vaccination season through December and even into January and beyond, because influenza disease often peaks during February and March, these efforts have not been successful to date. Any vaccine not used during the vaccination season must be discarded. Thus, there is a built-in disincentive for manufacturers to make more vaccine than they know they will sell and for

providers to order more vaccine than they know they can administer. Both can suffer substantial financial liability if they overproduce or over order, respectively.

Vaccine that becomes available after November is unlikely to be used. Even as we try to extend the influenza vaccination season, the goal should be to have all the vaccine projected to be needed available and distributed by October 1st or shortly thereafter.

Other programmatic challenges include the need to not simply provide information to the public and health care professionals but also the need to correct common misperceptions. For example, many members of the public and health care community mistakenly believe that the influenza shot can cause influenza, that it is not effective in prevention of influenza, and/or that vaccine is not indicated for them when in fact it is. The inactivated influenza vaccine contains both killed and disrupted virus and cannot cause influenza, itself. The live vaccine given as a spray in the nose may cause mild cold-like symptoms but not classical severe influenza. Influenza vaccines are effective against infections caused by the influenza virus. However, many respiratory illnesses are caused by other viruses. No protection is offered against these other viruses even though most refer to all of these conditions as "the flu". Influenza vaccine is recommended not only for the frail and elderly but also for healthy household contacts and healthy health care workers who come in contact with persons at high risk of complications from influenza to prevent exposure of these high risk persons to the virus.

For example, while influenza vaccine is beneficial to frail elderly persons in nursing homes, it is only about 30-40% effective in preventing illness. In contrast, vaccination of healthy workers in those same homes is 70-90% effective. Thus, vaccination of these health care workers could add substantial benefit to vaccination of the nursing home residents themselves by effectively reducing the chances that the health care workers get infected and spread the virus to the residents.

Finally, in contrast to childhood vaccination programs where the public sector plays a major role in control and distribution of vaccine, influenza vaccination of adults is primarily a private sector program. Less than 10% of influenza vaccines are purchased off of the Federal contract established by the CDC. Thus, the public sector has little leverage with regard to distribution and redistribution of vaccine during a shortage situation. The limited public sector infrastructure devoted to promotion of influenza vaccine is a barrier to developing the kinds of public/private sector partnerships necessary for collaboration in a shortage situation. Such collaboration is critical for assessing supplies at different levels of the system and redistributing vaccine, if needed from those with surpluses to those without adequate supplies.

The immediate cause of the recent shortage was bacterial contamination of vaccine prior to release from one of the two licensed manufacturers of inactivated influenza vaccine in the United States leading to only one producer distributing. However, there are a variety of underlying causes that over the years have made the United States vulnerable to influenza vaccine supply disruptions.

In 2000, there were four influenza vaccine manufacturers. Two were found to be in violation of compliance with current Good Manufacturing Practices (cGMP). One of these two companies

made the assessment that investments in their plant to bring them into compliance were not worthwhile and stopped distributing. The other manufacturer paid a fine and made improvements to come into compliance. They wound up distributing late and had some difficulties in selling all of their doses produced. This continued into the 2002-2003 season when that manufacturer was left with millions of doses that had to be discarded. Following the 2002-2003 season, this second manufacturer dropped out of the market leaving only two active distributors in the United States going into the 2003-2004 and 2004-2005 seasons. In addition, there was one manufacturer of a live attenuated nasal spray vaccine which produced limited quantities of vaccine.

Several factors decrease manufacturers' incentives to stay in the US market or enter the market. Vaccine produced but unsold at the end of the vaccination season must be discarded. The price of influenza vaccine is relatively low compared to other vaccines. While the catalogue price per dose has increased from about $2.15 during the 1997-1998 season to more than $8.00 per dose this season, it is still cheaper than any of the other routinely recommended vaccines. And there is a tension between increasing that price to obtain better return on investment and trying to increase market size from the 80-85 million doses that are distributed in good supply years to the more than 188 million doses that would be needed with full implementation of current influenza vaccine recommendations. Finally, the production process is complex and requires continued investments in plants to assure they are current with improving state of the art "Good Manufacturing Practices". Such investments require a good return on investment and minimization of risk for vaccine produced but not sold.

To reduce manufacturer risk and stimulate increased production, an influenza "buy-back" program is warranted for doses produced but not sold. Because any funds used in the buy back program are in essence "wasted" since they pay for doses that are discarded, and to attract manufacturers to the US market, a major Federal effort should be undertaken to increase demand for vaccine from the usual 80-85 million doses to close to the more than 188 million doses that would be needed for full implementation of vaccination of persons for whom influenza vaccine is already recommended. Demand generation should consist of an ongoing national, state, and local educational effort targeted to the health care community as well as the general public. Such an effort can be facilitated by developing an adult immunization Federal grant program for states and localities, modeled after the successful childhood 317 grant program. Funds should be provided for public sector infrastructure to implement efforts such as conducting outreach, developing and disseminating educational materials, providing technical assistance to providers to improve their immunization performance, and developing data systems to track vaccine distribution, use and to measure immunization coverage. In addition, a Federal Vaccines for Adults (VFA) should be established to provide free vaccines to uninsured adults, for whom influenza vaccine is currently recommended, in physician offices and other settings, working through State and local public health departments. This reduces risk to providers of ordering vaccine and not using it and provides incentives to uninsured patients to receive vaccines. This program also establishes a public/private partnership to improve immunization coverage for adults.

The major concern about the present problem is the potential for backsliding in our efforts to prevent the significant burden of influenza. While it is too early to tell if this season will be

mild, if it turns out to be, many of the people who might have received a vaccine in the past but were unable to receive it this year, may have a false sense of security that they do not need vaccine. Unfortunately, influenza is difficult to predict and if a mild season were to occur this year, it does not mean next year will also be mild.

If it turns out this season is moderate to severe, unfortunately many people who might have gained benefits from vaccination may suffer either because they did not seek vaccine or because they were unable to obtain it. One of the more effective strategies in reducing influenza is to reduce exposure of high risk persons to influenza by vaccinating their close contacts. Many more high risk persons may be exposed because their contacts were not vaccinated due to supply problems.

Given the shortage, could anything have been done differently to minimize its burden? I think CDC did the best it could under the circumstances. There was a need to prioritize vaccine and the priorities chosen by the experts on the Advisory Committee on Immunization Practices (ACIP) were reasonable. This meant delivering messages to others to forego vaccination. Unfortunately, there was a limited amount of live attenuated influenza vaccine for administration in the nose that could have been given to some persons who were not in the high risk groups that may now go unused. However, the quantities available of the live vaccine were not sufficient to meet usual demand. While there were clear messages suggesting the live vaccine as an alternative for those not in high risk groups, it was difficult to deliver that message in the face of the overall shortage and prioritization as evidenced by the fact that not all of the approximately 3 million doses of this vaccine were used this year. Since the live vaccine shows great promise of high effectiveness, I hope that it continues to be produced and distributed.

In conclusion, the influenza virus can cause a substantial health burden. Influenza vaccination is the best way to prevent this burden. The shortages are a result of lack of manufacturer incentives to enter and stay in the US market. Averting future shortages and averting the influenza burden involves providing incentives to manufacturers to produce vaccine, providers to order and administer it, and to the general public to seek and accept this lifesaving vaccine.

Table 1

Major Recommendations for Averting Influenza Vaccine Shortages in the Future

Minimize Manufacturer Risk

- Establish an influenza "back end guarantee" to compensate manufacturers for doses of vaccine above normal production that go unsold
- The Federal government would determine quantities of vaccine above usual production that it would guarantee

Increase Demand for Influenza Vaccine to Increase Market and Better Prevent Disease

- Establish an ongoing educational effort at national, state and local levels
- Establish an adult influenza immunization grant program to enhance infrastructure at the state and local levels
    - Outreach
    - Education
    - Data and tracking systems
    - Enhance provider immunization performance

- Establish a Federal "Vaccines for Adults" Program to purchase influenza vaccine doses for uninsured adults for whom influenza vaccine is recommended
    - Supply the vaccine through state and local health departments to public and private sector providers whom could administer it to their patients